REMARKS/ARGUMENTS

With this amendment, claims 10 and 12-32 are pending. Claims 1-22 are cancelled without prejudice to subsequent revival. For convenience, the Examiner's rejections are addressed in the order presented in the May 21, 2003, Office Action.

Applicants respectfully bring to the Examiner's attention that the presently claimed invention is directed to probes comprising MTAse exons that can be used to diagnose cancer by detecting the absence of catalytically active MTAse in a biological sample. For example, Applicants provide evidence that failure to detect MTAse exons correlates with failure to detect MTAse activity. (*See, e.g.*, Example IX, at page 34.) In addition, it is known that many malignant cells lack MTAse activity. (*See, e.g.*, page 2, lines 4-15.) Thus, the presently claimed probes are useful to detect MTAse deficient malignancies.

I. Status of the claims

Claims 1-22 are cancelled without prejudice to subsequent revival. New claims 23-38 are added.

New claims 23-38 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a specific MTAse nucleotide sequence or its complement, *i.e.*, probes. Support for stringent hybridization conditions is found at page 16, lines 10-22; and page 28, lines 8-22. Stringent hybridization is carried out in 1% SDS, 2 X SSC, 10% dextran sulfate, and 50% deionized formamide at 42°C; followed by three washes at room temperature for five minutes in 2 X SSC, a wash at 65°C for twenty minutes with 2 X SSC and 0.1% SDS, and a wash at room temperature for twenty minutes with 0.2 X SSC and 0.1% SDS. Stringent hybridization conditions are also defined to allow the autoradiographic detection of a target DNA to a single probe. Support for binding of a probe to the complement of a coding sequence is found, for example at page 11, lines 7-9 and at page 16, lines 10-14. Support for a probe that is less than 500 base pairs long is found, for example, at page 33, lines 9-10. These amendments add no new matter.

New claims 23 and 31 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a nucleotide sequence comprising nucleotides 2754-2894 of SEQ ID NO:1 or its complement. Support for nucleotides that specifically hybridize to MTAse encoding nucleic acids, *e.g.*, nucleotides 2754-2894 of SEQ ID NO:1 or its complement, is found throughout the specification, for example at page 4, lines 8-11; at page 33, lines 22-24; and at original claim 1. Dependent claims 24and 32 are directed to an isolated polynucleotide consisting of nucleotides 2754-2894 of SEQ ID NO:1. These amendments add no new matter.

New claims 25 and 33 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a nucleotide sequence comprising nucleotides 2838-2876 of SEQ ID NO:1 or its complement. Support for nucleotides that specifically hybridize to MTAse encoding nucleic acids, *e.g.*, nucleotides 2838-2876 of SEQ ID NO:1 or its complement, is found throughout the specification, for example at page 4, lines 8-11; at Figure 1; and at original claim 1. Dependent claims 26 and 34 are directed to an isolated polynucleotide consisting of nucleotides 2838-2876 of SEQ ID NO:1. These amendments add no new matter.

New claims 27 and 35 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a nucleotide sequence comprising nucleotides 2426-2548 of SEQ ID NO:1 or its complement. Support for nucleotides that specifically hybridize to MTAse encoding nucleic acids, *e.g.*, nucleotides 2426-2548 of SEQ ID NO:1 or its complement, is found throughout the specification, for example at page 4, lines 8-11; at Figure 1; and at original claim 1. Dependent claims 28 and 36 are directed to an isolated polynucleotide consisting of nucleotides 2426-2548 of SEQ ID NO:1. These amendments add no new matter.

New claims 29 and 37 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a nucleotide sequence comprising nucleotides 1764-1953 of SEQ ID NO:1 or its complement. Support for nucleotides that specifically hybridize to MTAse encoding nucleic acids, *e.g.*, nucleotides 1764-1953 of SEQ ID NO:1 or its complement, is found throughout the specification, for example at page 4, lines 8-11;

at Figure 1; and at original claim 1. Dependent claims 30 and 38 are directed to an isolated polynucleotide consisting of nucleotides 1764-1953 of SEQ ID NO:1. These amendments add no new matter.

New claims 31-38 are directed to isolated polynucleotides, less than 500 basepairs long, that hybridize under stringent conditions to a nucleotide sequence comprising an exon of MTAse or its complement, wherein the polynucleotide is used to determine methylthioadenosine phosphorylase (MTAse) deficiency in a biological sample. Support for use of probes that hybridize to MTAse exons to determine an MTAse deficiency is found throughout the specification, for example at page 4, lines 8-11; and at original claim 1. Support for a biological sample is found throughout the specification, for example, at page 7, lines 12-16.

II. New Matter

Claims 17-22 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the application at the time of filing. According to the Office Action, the nucleotide sequences of exons 4-8 were not part of the priority application as originally filed in December 1993, and thus, nucleotide sequences that hybridize to exons 4-8 were allegedly not part of the originally filed application.

To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection. The amended claims are now directed to nucleotide sequences that hybridize to exons 6-8 Applicants submit that exons 6-8 were disclosed in the priority application, as well as nucleotide sequences that hybridize to them.

In both the priority application and the current application, exons are disclosed in figure 1 as underlined sequence. Exon 6 is currently claimed as nucleotides 1764-1953 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 964-1203 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document. Exon 7 is currently claimed as nucleotides 2426-2548 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 1640-1762 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document. Exon 8 is currently claimed as nucleotides 2838-2876 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 2272-2310 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document.

In view of the above amendments and remarks, Applicants respectfully request that the rejection for alleged entry of new matter by withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 17-22 are rejected as allegedly containing subject matter that was not described in the specification as originally filed. In the Office Action, the Examiner observed that the purpose of the written description requirement is to convey to one of skill in the art that the inventor was in possession of the invention as of the filing date. The rejection then stated that claims encompass full length cDNA, introns, and the MTAse gene including regulatory regions.

To the extent the rejection applies to the claims as amended, Applicants respectfully traverse this rejection. The claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The claims set forth both functional elements as well as structural elements, i.e., hybridization conditions and reference sequences to which members of the claimed genus hybridize. Therefore, the claimed sequences are thereby defined via shared physical and structural properties.

As described above, the present invention relates to the discovery of genomic DNA sequences that include exons of the MTAse gene and that function to detect deletions of the MTAse gene that are associated with cancer. The genus of MTAse exons and nucleic acids that hybridize to those exons is claimed by reference to shared structural features, *i.e.*, nucleic acid sequences of nucleotides 2754-2894 of SEQ ID NO:1 and its complement (exon 8 and adjacent sequence), nucleotides 2838-2876 of SEQ ID NO:1 and its complement (exon 8), nucleotides 2426-2548 of SEQ ID NO:1 and its complement (exon 7), and 1764-1953 of SEQ

ID NO:1 and its complement (exon 6). The claims also provide hybridization conditions in which the claimed genus of nucleic acids hybridize to the reference sequences.

The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*). Moreover, in the same light, the percent identity of a nucleic acid to a reference sequence is a structural feature, as it relies entirely on the sequence of the molecule.

In the present application, Applicants have provided reference nucleotide sequences, as well as hybridization conditions. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the claimed genus. The conserved sequences encoding structural features of the genus, and the given conditions under which the claimed genus would hybridize to such reference sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed". (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). The specification thus appropriately describes the claimed nucleic acid genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*. As such, Applicants respectfully request that the Examiner withdraw the rejection.

IV. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 17-22 are rejected as allegedly claiming subject matter that is not enabled by the specification. Furthermore, the Examiner is apparently concerned about inoperable embodiments. *See, e.g.*, Office Action, page 7. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice an invention is determined by considering factors such as the amount of guidance presented in the application, the state of the prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The rejection alleges that the specification provides enablement only for a nucleic acid consisting of SEQ ID NO:1, but not for nucleic acids that hybridize to specific exons of MTAse as depicted in Figure 1. However, the claims recite both functional and structural characteristics of the MTAse nucleic acids of the invention. The present application also provides functional assays for identification of MTAse nucleic acids without undue experimentation. The assays and examples of the specification, together with standard methodology known to those of skill in the art, therefore provide adequate guidance for identifying claimed MTAse nucleic acids.

The assertion of undue experimentation appears to be based on an assumption that enablement requires the description of each and every nucleic acid that could be covered in the invention. This requirement is not consistent with the patent laws. Indeed, it is well settled in the biotechnology art that routine screening of even large numbers of samples is not undue experimentation when a probability of success exists. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Using the conditions set forth in the claims and specification and routine methodology, any competent laboratory technician in a molecular biology laboratory could identify nucleic acids that hybridize to the reference sequences recited in the claims. As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments." In the present case, one of skill, given the reference nucleotide sequences and the specified hybridization conditions, could easily screen for other nucleic acid molecules that fall within the scope of the claims.

The present invention describes a family of nucleic acids probes that function to identify deletions in the MTAse gene and that are defined structurally by hybridize to reference nucleic acids.

At the time of the present invention, identification of nucleic acids having the functional and structural characteristics described above was well within the means of one of skill of the art, without undue experimentation. The present specification provides working examples and discloses standard techniques known to those of skill in the art, for the identification of functional MTAse nucleic acids that hybridize to reference sequences and can be used to detect genomic deletions in the MTAse gene.

The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for nucleic acids having the structural and functional characteristics described above is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants therefore respectfully request that the rejection be withdrawn.

The claimed nucleic acids probes are less than 500 base pairs long. Applicants submit that methods were well known to those of skill in the art at the time filing to determine the length of a nucleic acid. In addition, Applicants also submit that the definition of stringent hybridization conditions includes a requirement for specific binding to the reference sequence, *i.e.*, the probe (MTAse nucleic acid) will bind to a unique sequence in a heterogeneous mixture of nucleic acids. (Specification at page 16, lines 18-22.) Those of skill will recognize that, at the time of filing, the requirement for specific binding excludes very short polynucleotides, and in addition, that assays were available in the art to test probes for their ability to bind to a single sequence within a heterogeneous mixture of nucleic acids.

The specification, combined with the state of the prior art, thus provides a number of different assays demonstrating that any experimentation required to identify the claimed MTAse nucleic acids is not undue. *In re Wands*, 8 USPQ 1400 (Fed. Cir. 1988). Applicants respectfully request that the rejection be withdrawn.

V. Priority

The Office Action maintains the date of priority of claims 17-22 as March 26, 1997. To the extent the priority decision applies to the claims as amended, Applicants respectfully traverse the rejection.

The amended claims are now directed to nucleotide sequences that hybridize to exons 6-8 Applicants submit that exons 6-8 were disclosed in USSN 08/176,855 priority application, as well as nucleotide sequences that hybridize to them. USSN 08/176,855, *i.e.*, the priority application, was filed on December 29, 1993 and that date is the priority date of the application.

In both the priority application and the current application, exons are disclosed in figure 1 as underlined sequence. Exon 6 is currently claimed as nucleotides 1764-1953 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 964-1203 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document. Exon 7 is currently claimed as nucleotides 2426-2548 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 1640-1762 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document. Exon 8 is currently claimed as nucleotides 2838-2876 of SEQ ID NO:1, and in the priority document was disclosed as nucleotides 2272-2310 of SEQ ID NO:1, *i.e.*, figure 1 of the priority document.

In view of the above amendments and remarks, Applicants respectfully request that the application be given the priority date of December 29, 1993.

VI. Rejections under 35 U.S.C. §102(b)

Claims 17-22 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Olopade *et al* (PNAS 92:6489-6493 (1995)). The Office action bases the rejection, at least in part, on maintenance of a priority date of March 26, 1997.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited references must contain every element of the claims at issue.

To the extent the Office Action applies to the claims as amended, Applicants respectfully traverse the rejection. As described above the amended claims are directed to exons 6, 7, and 8, and to an additional sequence including exon 8 and adjacent genomic sequence. Each of these sequences was disclosed in the earliest priority document, USSN 08/176,855, filed December 29, 1993, well before the date of publication of Olopade *et al.* Thus, Olopade, *et al.* does not anticipate the amended claims.

However, even if the priority date of March 26, 1997 is maintained, Olopade *et al.* cannot anticipate the claims, because Olopade *et al.* does not disclose all the elements of the now-claimed invention. The amended claims are directed to nucleic acid sequences less than 500 base pairs long that hybridize to exons 6, 7, or 8, or a nucleic acid sequence that includes exon 8 and adjacent genomic sequence. Olopade *et al.* does not disclose any MTAse exons or nucleic acids less than 500 base pairs long that hybridize to them. Thus, Olopade *et al.* does not disclose all the elements of the claimed invention and does not anticipate the claims.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

VII. Rejections under 35 U.S.C. §102(a)

Claims 17-22 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Nobori *et al* (PNAS 93:6203-6208 (June, 1996)). The Office action bases the rejection, at least in part, on maintenance of a priority date of March 26, 1997. As above, in order to anticipate, the cited references must contain every element of the claims at issue.

To the extent the Office Action applies to the claims as amended, Applicants respectfully traverse the rejection. As described above the amended claims are directed to exons 6, 7, and 8, and to an additional sequence including exon 8 and adjacent genomic sequence. Each of these sequences was disclosed in the earliest priority document, USSN 08/176,855, filed December 29, 1993, well before the date of publication of Nobori *et al.* Thus, Nobori, *et al.* does not anticipate the amended claims.

However, if the priority date of March 26, 1997 is maintained, Applicants respectfully traverse the rejection and assert that the reference cited by the Examiner is the

inventors' own work and is improperly cited against them under 35 U.S.C. §102(a). The other individuals listed as authors of Nobori *et al.* did not make inventive contributions to the claimed subject matter. A declaration to that effect is included as Exhibit A. An executed copy will be forwarded upon our receipt.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

VIII. Rejection for alleged Double Patenting

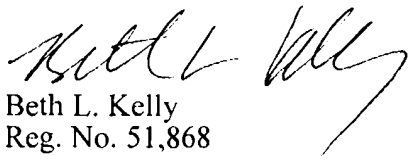
Claims 17-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7and 9 of U.S. Patent No. 5,942,393. Applicants submit that claims 17 and 22 are now cancelled. However, in order to expedite prosecution, if the double patenting rejection is maintained for the amended claims, Applicants will file a terminal disclaimer to overcome the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments: RCE
Decl. of Inventorship Exhibit A
Petition to Extend Time (2 mth.)
Fee Transmittal

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